ARTICLES

Geographic Variation in Mortality From Breast Cancer Among White Women in the United States

*Susan R. Sturgeon, Catherine Schairer, Mitchell Gail, Mary McAdams, Louise A. Brinton, Robert N. Hoover**

Background: **For several decades, mortality from breast cancer has been higher in the northeastern part of the United States than in other regions, particularly the South. Rates have also been somewhat higher in the Midwest and West than in the South, especially among older women. The reasons for these geographic variations are not well understood.** ***Purpose:*** **The objective of this study was to evaluate geographic differences in U.S. breast cancer mortality rates in 1987, after taking into account regional differences in the distribution of recognized breast cancer risk factors (e.g., late age at first live birth) and certain prognostic factors (e.g., mammography use).** ***Methods:*** **The 1987 breast cancer mortality rates for four regions of the country were obtained from the National Center for Health Statistics. Regional data on the distribution of breast cancer risk factors were obtained from 1987 National Health Interview Cancer Epidemiology Supplement interviews with 9778 white women aged 20-79 years. Regional data on the distribution of mammography use were obtained from 1987 National Health Interview Cancer Control Supplement interviews with 3795 white women aged 50-79 years.** ***Results:*** **Age-adjusted mortality ratios (MRs) among women 50 years and older were 1.15, 1.18, and 1.30 in the West, Midwest, and Northeast, respectively, compared with the South. Corresponding MRs among women 20-49 years old were 1.01, 1.08, and 1.07 in the West, Midwest, and Northeast, respectively, compared with the South. After adjustment for recognized risk factors and certain prognostic factors, MRs among older women were 1.13 (95% confidence interval [CI] = 1.04-1.23), 1.08 (95% CI = 1.01-1.16), and 1.13 (95% CI = 1.04-1.23) in the West, Midwest, and Northeast, respectively, compared with the South. Corresponding MRs among younger women were 0.94 (95% CI = 0.76-1.16), 1.05 (95% CI = 0.92-1.18), and 0.99 (95% CI = 0.86-1.14), respectively.** ***Conclusion:*** **Before adjustment for regional differences in recognized risk factors and prognostic factors, mortality excesses among younger women in the Northeast, Midwest, and West were less than 10% compared with the South. After adjustment, MRs were near unity for all regions. Among older women, the excess mortality was more substantial before adjustment for relevant factors, ranging from 15% in the West to 30% in the Northeast. Approximately 50% of the excesses in the Northeast and Midwest and 10% of the excess in the West could be explained on the basis of regional differences in the prevalence of recognized breast cancer risk factors and prognostic factors. After adjustment for these factors, the magnitude of excess in breast cancer mortality in the Northeast (13%) was comparable to that in the West (13%) but still slightly higher than that in the Midwest (8%). [J Natl Cancer Inst 1995;87:1846-53]**

For at least several decades, mortality from breast cancer has been higher in the northeastern part of the United States than in the other regions of the country, particularly the South. Mortality rates from breast cancer have also been somewhat higher in the Midwest and West than in the South, particularly among older women (*1*). The reasons for this geographic variation are not well understood. One study (*2*) has suggested that delayed childbearing could explain some of the excess mortality from breast cancer in the Northeast, but few data are available on the role of other recognized risk factors and prognostic factors.

The objective of this study was to evaluate geographic differences in U.S. breast cancer mortality rates in 1987, after taking into account regional differences in the distribution of recognized breast cancer risk factors (e.g., late age at first live

**Affiliations of authors:* S. R. Sturgeon, C. Schairer, M. Gail, L. A. Brinton, R. N. Hoover, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; M. McAdams, Information Management Services, Inc., Silver Spring, MD.

Correspondence to: Susan R. Sturgeon, Dr. P.H., National Institutes of Health, Executive Plaza North, Rm. 443, Bethesda, MD 20892.

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birth and family history of breast cancer) and certain prognostic factors (e.g., mammography use).

Methods

Data Sources

Table 1 summarizes data sources used in this analysis. Unadjusted 1987 mortality rates of breast cancer for white women in four regions of the country were obtained from the National Center for Health Statistics (NCHS) (*3*). The four regions corresponded to those used by the U.S. Bureau of the Census (Table 2).

Regional prevalence data on breast cancer risk factors and certain prognostic factors were derived from the 1987 National Health Interview Survey (NHIS) (*3*). The NHIS is a household survey administered yearly to a representative sample of the civilian, noninstitutionalized U.S. population. It consists of a basic health and sociodemographic section that remains the same each year and special topic supplements that change from year to year. In 1987, one adult, 18 years of age or older, was randomly selected from each NHIS household to receive either the self-administered Cancer Epidemiology Supplement (CES) or the Cancer Control Supplement (CCS). The response rate for the household survey was 95.3%, with a total of 47 240 households containing 122 859 persons completing the basic questionnaire. From these eligible households, a total of 22 080 adults completed a CES questionnaire and 22 043 completed a CCS questionnaire. The total of 44 123 completed interviews represents approximately 86% of the identified eligible subjects. The NHIS was approved by the human subjects committee of the NCHS, and informed consent was obtained from all participants in the survey.

The present analysis was based on CES interviews with 9778 white women between the ages of 20 and 79 years. Supplemental information on the regional prevalence of mammography use was based on CCS interviews with 3795 white women between the ages of 50 and 79 years. This initial analysis was limited to white women because they constituted the overwhelming majority of women who completed the CES and CCS questionnaires.

Separate estimates of the regional prevalence of breast cancer risk factors and other prognostic factors were derived from the CES for white women between the ages of 20 and 49 years and between the ages of 50 and 79 years. Data from the CES were used to estimate the percentage of women between the ages of 20 and 49 years and 50 and 79 years who were as follows: 1) premenopausal, 2) naturally menopausal before age 45 years, 3) surgically menopausal before age 45 years, and 4) all other women. Data from the CES, however, were insufficient to distinguish between women with at least one ovary conserved and those who had a bilateral oophorectomy. The latter surgery reduces breast cancer risk in younger women (*4*), so we used supplemental data from the 1988 National Hospital Discharge Survey to estimate the percentage of women aged 45 years and younger in each region who had both ovaries removed at the time of surgical menopause (*5*). Because of the way the ovarian status was determined, however, this variable could not be examined in combination with the other risk factor information. Furthermore, the mammography variable could not be examined in combination with the other risk factor information because different women responded to the CCS and CES.

Data Analysis

The adjusted mortality ratio (MR) is calculated from

$$\frac{R_1\Sigma(n_{2j}\,RR_j/n_2)}{R_2\Sigma(n_{1j}\,RR_j/n_1)}, \qquad [1]$$

where the summation is over the strata defined by all combinations of the risk factors, $j = 1$ to $j = N$; R_1 = the unadjusted mortality rate of breast cancer in the comparison region; R_2 = the unadjusted mortality rate of breast cancer in the reference region (South); n_1 = total number of white women in the comparison region; n_2 = total number of white women in the reference region, n_{1j} = number of white women in stratum j in the comparison region; n_{2j} = number of white women in stratum j in the reference region; and RR_j = relative risk comparing the risk among those in stratum j with the risk among those at the referent (lowest) level of all risk factors.

The adjusted MR can be interpreted as the unadjusted MR that would be expected if the comparison region had the same proportion of women with the specified risk factors as the reference region (South). An analogous calculation based on risk factor prevalence data from breast cancer cases, rather than the entire population, was used in an analysis by Dean et al. (*6*).

Prevalence data from the NHIS are representative of the noninstitutionalized U.S. civilian population, whereas breast cancer mortality rates obtained from the NCHS are based on the entire U.S. population. To address this issue in the analysis, we reweighted the age distribution of the NHIS for each region to 1987 population data from the U.S. Bureau of the Census.

Confidence intervals (CIs) for the adjusted MR were obtained from $\exp\{\log(MR) \pm 1.96\ \hat{\sigma}\}$, where $\hat{\sigma}^2$ is the estimated variance of log(MR). The quantity $\hat{\sigma}^2$ is estimated as $1/D_1 + 1/D_2 + V_1(\Sigma n_{1j}\,RR_j/n_1)^{-2} + V_2(\Sigma n_{2j}\,RR_j/n_2)^{-2}$, where D_1 and D_2 are the numbers of deaths in regions 1 and 2 (reference), respectively, and where V_1 and V_2 are the variances of the sums in the

Table 1. Summary of data sources and types of data used in this analysis

Data sources	Types of data
National Center for Health Statistics (NCHS)*	1987 breast cancer mortality rates
1987 National Health Interview Survey (NHIS)†	% distribution of breast cancer risk factors and prognostic factors by region
Cancer Epidemiology Supplement (CES)‡	Age Age at menarche First-degree relative with breast cancer Biopsy-proven benign breast disease Age at first live birth Body mass index Alcohol intake Age at menopause Education Menopausal estrogen use
Cancer Control Supplement (CCS)‡	Mammography
National Hospital Discharge Survey (NHDS)§	% distribution of ovarian status by region

*NCHS provided data on unadjusted 1987 mortality rates of breast cancer for white women in four regions. (*see* Table 2 for U.S. Bureau of the Census regional definitions) of the country.

†NHIS is a household survey administered yearly to a representative sample of the civilian, noninstitutionalized U.S. population that consists of a basic health and sociodemographic section that remains the same each year and special topic supplements that change from year to year.

‡In 1987, one adult (aged 18 years or older) was randomly selected from each NHIS household to receive either the self-administered CES or the CCS. From a total of 47 240 eligible households (95.3% response rate for household survey), a total of 22 080 adults completed a CES questionnaire and a total of 22 043 adults completed a CCS questionnaire. A total of 44 123 completed interviews representing approximately 86% of the identified eligible subjects.

§Supplemental data from the 1988 NHDS was used to estimate the percentage of women aged 45 years and younger in each region who had both ovaries removed at the time of surgical menopause.

Table 2. Regional definitions from the U.S. Bureau of the Census

	Definition
South	Delaware, Maryland, District of Columbia, West Virginia, Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Oklahoma, Arkansas, Texas.
West	Washington, Oregon, California, Nevada, New Mexico, Arizona, Idaho, Utah, Colorado, Montana, Wyoming, Alaska, Hawaii.
Midwest	Ohio, Illinois, Indiana, Michigan, Wisconsin, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas.
Northeast	Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania.

denominator and numerator of equation 1, respectively. The quantities V_1 and V_2 were estimated with the use of the jackknife method for stratified cluster samples (*7*). The relative risks, RR_j, in equation 1 are assumed to be known constants.

For each region of the country with at least a 10% age-adjusted mortality excess compared with the South (i.e., $MR_1 \geq 1.10$), the percentage of the mortality excess that was explained by established breast cancer risk factors and certain prognostic factors was calculated from $[MR_1 - MR_2]/[MR_1 - 1]$ (*2*), where MR_1 = the MR from the age-adjusted model and MR_2 = the MR from the fully adjusted model.

Relative Risks

Mortality relative risks (RRs) for most recognized breast cancer risk factors are not widely available in the literature. Incidence RRs were used in this analysis for risk factors that have not been convincingly demonstrated to affect survival from breast cancer, including age at first live birth, age at menarche, age at menopause, and family history of breast cancer (*8-15*) (Table 3). Incidence RRs were also used for alcohol intake and biopsy-proven benign breast disease, two factors that have not been examined in relation to survival. Mortality RRs were estimated from available data for risk factors that have been shown to affect survival from breast cancer (i.e., age, body mass index, education, and mammography use) (*13,16-18*). Mortality RRs were also estimated for menopausal estrogen use because it has been found to be associated with an increased risk of breast cancer incidence but an unexpected decreased risk of death from breast cancer (*19*). Because of the controversial nature of this association, however, multivariate adjusted MRs are provided both with and without this variable.

Incidence RRs for age at menarche, a first-degree relative with breast cancer, alcohol intake, and age at menopause were derived from multivariate analyses of the Breast Cancer Detection Demonstration Project (BCDDP) case–control study (*20-22*). Incidence RRs for biopsy-proven benign breast disease were estimated from multivariate analyses of the BCDDP Follow-Up Study (*23*). Incidence RRs for age at first live birth were obtained from a multivariate analysis of a case–control study by MacMahon et al. (*24*). We conducted a literature review of other breast cancer studies and found these estimates to be similar to those observed in most studies.

Mortality RRs for age were obtained from 1987 breast cancer mortality rates provided by the NCHS. Mortality RRs for mammography use were estimated from clinical studies (*17*), and those for body mass (kg/m^2) and education, adjusted for recognized breast cancer risk factors, were obtained from an unpublished multivariate analysis of data from the BCDDP Follow-Up Study (*25*). Results from a multivariate analysis of the Nurses' Health Study were used to derive mortality RRs for menopausal estrogen use (*26*).

Multivariate mortality RRs, RR_j, were obtained by multiplying estimated RRs for corresponding levels of each component risk factor. This procedure is justified by the fact that most component RRs were estimated with adjustment for other important risk factors and by the assumption that interactions among risk factors are negligible.

Results

NHIS Risk Factor Prevalence Data by Region

Table 4 presents the prevalence of individual risk factors by region among white women younger than age 50 years. The prevalence of several risk factors, including older age, earlier age at menarche, a history of a first-degree relative with breast cancer, biopsy-proven benign breast disease, and high body mass index were generally similar in the four regions. However, the distributions of age at first live birth, alcohol intake, and age at menopause varied in the direction that adjustment for these factors would tend to decrease rates in other regions compared with the South. For example, only 17.1% of women in the South had their first birth after age 24 years compared with 18.7%, 18.6%, and 23.2% of women in the West, Midwest, and Northeast, respectively. By contrast, regional differences in years of

Table 3. Magnitude and source of relative risks (RRs) used in the models

Risk factor	RRs	Source of estimates (Ref. No.)*
Age, y†		NCHS
20-29	1.0‡	
30-39	13.5	
40-49	46.2	
50-59	1.0‡	
60-69	1.5	
70-79	1.9	
Age at menarche, y§		(*20*)
≥14	1.0‡	
12-13	1.1	
<12	1.2	
First-degree relative with breast cancer§		(*23*)
No	1.0‡	
Yes	2.0	
Biopsy-proven benign breast disease§		(*21*)
No	1.0‡	
Yes	1.7	
Age at first live birth, y§		(*24*)
<20	1.0‡	
20-24	1.2	
25-29	1.6	
30-34	1.9	
≥35	2.4	
Nulliparous	2.0	
Body mass index, kg/m^2†		(*25*)
<21.5	1.0‡	
21.5-23.3	1.0	
23.4-26.2	1.1	
≥26.3	1.4	
Alcohol intake, g/wk§		(*22*)
None	1.0‡	
<14	1.1	
14-92	1.1	
93-182	1.3	
≥183	1.7	
Age at menopause§		(*20*)
Premenopausal	1.7	
Natural menopause before age 45 y	1.2	
Bilateral oophorectomy before age 45 y	1.0‡	
Other	1.4	
Education, y†		(*25*)
<12	2.0	
12	1.6	
13-15	1.4	
≥16	1.0‡	
Menopausal estrogen use†		(*26*)
Yes	1.0‡	
No	1.3	
Mammogram history†		(*17*)
Never had mammogram	1.4	
Had only routine mammograms	1.0‡	
Had mammogram at least once for a problem	1.3	

*National Center for Health Statistics.

†Mortality RRs were estimated from available data for risk factors that have been shown to affect survival from breast cancer (i.e., age, body mass index, education, and mammography use). Mortality RRs were also estimated for menopausal estrogen use because it has been found to be associated with an increased risk of breast cancer incidence but an unexpected decreased risk of death from breast cancer. Because of the controversial nature of menopausal estrogen use, multivariate adjusted mortality RRs are provided both with and without this variable.

‡Referent group.

§Incidence RRs were used in this analysis for risk factors that have not been convincingly demonstrated to affect survival from breast cancer, including age at first live birth, age at menarche, age at menopause, and family history of breast cancer. Incidence RRs were also used for alcohol intake and biopsy-proven benign breast disease, two factors that have not been examined in relation to survival.

Table 4. Region-specific prevalence (%) of factors that influence breast cancer mortality among white women aged 20-49 years

	Region			
	South	West	Midwest	Northeast
Age, y*				
20-29	37.2	37.2	37.8	37.4
30-39	35.9	37.5	36.1	35.6
40-49	26.9	25.3	26.1	27.0
Age at menarche, y				
≥14	27.5	24.3	24.6	25.8
12-13	53.7	59.1	57.2	54.5
<12	18.8	16.6	18.3	19.8
First-degree relative with breast cancer	3.9	5.2	3.8	4.0
Biopsy-proven benign breast disease	6.1	5.1	6.3	5.7
Age at first live birth, y				
<20	24.0	20.2	20.3	15.6
20-24	31.7	29.4	31.5	28.8
25-29	13.6	13.3	15.0	18.0
30-34	2.7	4.8	3.0	4.2
≥35	0.8	0.6	0.6	1.0
Nulliparous	27.1	31.7	29.6	32.4
Body mass index, kg/m^2				
<21.5	37.8	40.1	36.5	35.5
21.5-23.3	23.4	21.9	20.8	24.6
23.4-26.2	16.1	16.1	18.9	18.5
≥26.3	22.7	21.9	23.8	21.5
Alcohol intake, g/wk				
None	34.1	22.7	20.5	25.7
<14	35.7	36.2	39.6	36.0
14-92	21.6	28.4	29.4	28.1
93-182	5.5	8.8	6.7	7.1
≥183	3.1	4.0	3.9	3.2
Age at menopause				
Premenopausal	85.3	90.1	89.9	93.4
Bilateral oophorectomy before age 45	8.3	6.7	4.8	3.3
Natural menopause before age 45	0.9	0.5	0.8	0.9
Other menopause	5.5	2.8	4.5	2.4
Education, y				
<12	17.7	15.0	9.8	11.7
12	41.1	34.9	45.5	40.9
13-15	22.0	28.9	24.4	22.7
≥16	19.3	21.2	20.3	24.7

*Reweighted using population estimates from the National Center for Health Statistics.

Table 5. Region-specific prevalence (%) of factors that influence breast cancer mortality among white women aged 50-79 years

	Region			
	South	West	Midwest	Northeast
Age, y*				
50-59	36.7	37.3	36.3	35.4
60-69	36.7	37.0	36.5	37.2
70-79	26.6	25.7	27.2	27.4
Age at menarche, y				
≥14	36.2	35.7	38.6	34.7
12-13	48.2	48.8	47.4	48.7
<12	15.6	15.4	14.0	16.5
First-degree relative with breast cancer	6.7	10.0	9.4	7.9
Biopsy-proven benign breast disease	14.2	14.6	12.4	11.9
Age at first live birth, y				
<20	22.4	20.7	16.5	11.0
20-24	41.5	40.0	41.1	37.0
25-29	15.5	19.7	20.7	23.1
30-34	5.2	6.0	5.7	8.2
≥35	1.5	1.6	2.6	3.5
Nulliparous	14.1	12.0	13.5	17.2
Body mass index, kg/m^2				
<21.5	21.8	23.4	17.0	16.0
21.5-23.3	18.2	22.5	19.3	20.4
23.4-26.2	26.3	23.9	23.3	24.0
≥26.3	33.7	30.1	40.3	39.6
Alcohol intake, g/wk				
None	59.6	36.5	44.8	44.1
<14	23.3	29.2	32.1	31.3
14-92	11.5	24.2	15.3	15.2
93-182	2.8	5.8	3.6	6.7
≥183	2.9	4.3	4.2	2.8
Age at menopause				
Premenopausal	6.9	10.0	5.3	7.0
Bilateral oophorectomy before age 45 y	11.3	11.1	8.4	7.7
Natural menopause before age 45 y	10.2	7.3	8.7	10.3
Other menopause	71.5	71.7	77.6	74.9
Menopausal estrogens	38.8	52.5	34.1	25.2
Education, y				
<12	37.3	22.4	31.4	31.1
12	39.3	43.4	46.1	46.6
13-15	14.1	21.6	12.3	12.5
≥16	9.3	12.6	10.3	9.7
Mammogram				
Never	64.0	52.2	58.1	63.0
Ever	36.0	47.8	41.9	37.0
All routine	23.4	34.5	30.1	25.7
At least one not routine	12.7	13.3	11.8	11.3

*Reweighted using population estimates from the National Center for Health Statistics.

education were such that adjustment for education would tend to increase rates in other regions compared with the South. The percentages of women who had completed less than a college education were 80.8% in the South, 78.8% in the West, 79.7% in the Midwest, and 75.3% in the Northeast.

Table 5 presents the prevalence of individual risk factors by region for white women aged 50 years and older. The distributions of age, age at menarche, having a first-degree relative with breast cancer, and having biopsy-proven benign breast disease varied only slightly across regions. Prevalences of age at first live birth, body mass index, alcohol intake, age at menopause, and menopausal estrogen use varied more substantially across regions in a manner that adjustment for them would tend to decrease rates in other regions relative to the South. For example, the percentage of women who had a first birth after age 24 years ranged from 22.2% in the South to 34.8% in the Northeast. By contrast, differences in the prevalences of education and mammography use were such that adjustment for these factors would tend to increase rates in other regions relative to the South. For example, the percentage of women without a high school education ranged from 37.3% in the South to 22.4% in the West.

Adjusted Breast Cancer MRs for Women Younger Than Age 50 Years

Unadjusted 1987 breast cancer mortality rates per 100 000 for white women between ages 20 and 49 years were 10.4, 10.2, 11.0, and 11.1 in the South, West, Midwest, and Northeast, respectively. The corresponding unadjusted MRs were 0.98, 1.06, and 1.07 in the West, Midwest, and Northeast, respectively (Table 6). After adjustment for age alone, MRs were 1.01, 1.08, and 1.07 in the West, Midwest, and Northeast, respectively. Results were the same when mortality RRs for 5-year age categories were used. Age-adjusted MRs in the West, Midwest, and Northeast changed little after additional adjustment for age at menarche, a first-degree relative with breast cancer, biopsy-proven benign breast disease, and body mass index. Because of regional differences in the distribution of age at first live birth, however, adjustment for this risk factor resulted in decreases in the MRs from 1.01 to 0.96 in the West and from 1.07 to 1.00 in the Northeast. Adjustment for age at menopause and alcohol intake also resulted in small decreases in the MRs in the West, Midwest, and Northeast. By contrast, adjustment for education led to increases in the MRs from 1.01 to 1.06 in the West, from 1.08 to 1.11 in the Midwest, and from 1.07 to 1.10 in the Northeast. The final MRs, adjusted for all factors, except age at menopause, were 0.94 (95% CI = 0.76-1.16), 1.05 (95% CI = 0.92-1.18), and 0.99 (95% CI = 0.86-1.14) in the West, Midwest, and Northeast, respectively. Had we been able to include age at menopause in our final model, the magnitude of the MRs in the Midwest and Northeast would most likely have been slightly lower than those presented above.

Adjusted Breast Cancer MRs for White Women Aged 50 Years and Older

Unadjusted 1987 breast cancer mortality rates per 100 000 for women between the ages of 50 and 79 years were 80.7, 91.8, 95.0, and 105.9 in the South, West, Midwest, and Northeast, respectively. These rates correspond to unadjusted MRs of 1.14, 1.18, and 1.31 for the West, Midwest, and Northeast, respectively (Table 7). After adjustment for age alone, the corresponding MRs were essentially the same. Results were identical when mortality RRs for 5-year age categories were used. Individual adjustment for a first-degree relative with breast cancer, biopsy-proven benign breast disease, body mass index, alcohol use, and age at menopause led to small changes in the MRs for the West, Midwest, and Northeast. Because of more substantial regional differences in the distribution of age at first live birth, the MRs decreased from 1.15 to 1.13 in the West, from 1.18 to 1.13 in the Midwest, and from 1.30 to 1.19 in the Northeast after adjustment for this risk factor. The MR for the West increased from 1.15 to 1.21 and from 1.15 to 1.18 after adjustment for education and mammography use, respectively. The MR for the Northeast, however, remained essentially unchanged after adjustment for either education or mammography. Adjustment for menopausal estrogen use also resulted in an increase in the MR from 1.15 to 1.19 for the West but a decrease in the MR from 1.30 to 1.26 in the Northeast. The final MRs, adjusted for all factors except age at menopause, mammography use, and menopausal estrogen use, were 1.13 (95% CI = 1.04-1.23), 1.08 (95% CI = 1.01-1.16), and 1.13 (95% CI = 1.04-1.23) for the West, Midwest, and Northeast, respectively. The corresponding percentages of the mortality excess that were explained by the

Table 6. Regional breast cancer mortality ratios among white women, aged 20-49 years, before and after adjustment for recognized breast cancer risk factors and certain prognostic factors

	Region			
Risk factor	South*	West	Midwest	Northeast
Unadjusted	1.0	0.98	1.06	1.07
Age alone	1.0	1.01	1.08	1.07
Age, age at menarche	1.0	1.00	1.07	1.06
Age, first-degree relative	1.0	0.98	1.07	1.05
Age, biopsy-proven benign breast disease	1.0	1.02	1.08	1.07
Age, age at first live birth	1.0	0.96	1.06	1.00
Age, alcohol	1.0	0.98	1.05	1.05
Age, body mass index	1.0	1.01	1.06	1.07
Age, education	1.0	1.06	1.11	1.10
Age at menopause alone	1.0	0.97	1.04	1.04
Age, age at menarche, first-degree relative, biopsy-proven benign breast disease, age at first live birth, alcohol, body mass index, education	1.0	0.94	1.05	0.99
95% confidence interval for full model		0.76-1.16	0.92-1.18	0.86-1.14

*Reference region.

Table 7. Regional breast cancer mortality ratios among white women, aged 50-79 years, before and after adjustment for recognized breast cancer risk factors and certain prognostic factors

	Region			
Risk factor	South*	West	Midwest	Northeast
Unadjusted	1.0	1.14	1.18	1.31
Age alone	1.0	1.15	1.18	1.30
Age, age at menarche	1.0	1.14	1.17	1.30
Age, first-degree relative	1.0	1.11	1.14	1.28
Age, biopsy-proven benign breast disease	1.0	1.14	1.20	1.33
Age, age at first live birth	1.0	1.13	1.13	1.19
Age, body mass index	1.0	1.16	1.15	1.27
Age, alcohol	1.0	1.10	1.15	1.28
Age at menopause alone	1.0	1.12	1.17	1.30
Age, education	1.0	1.21	1.18	1.32
Age, mammography	1.0	1.18	1.20	1.31
Age, menopausal estrogens	1.0	1.19	1.16	1.26
Age, age at menarche, first-degree relative, biopsy-proven benign breast disease, age at first live birth, body mass index, alcohol, education	1.0	1.13	1.08	1.13
95% confidence interval for full model		1.04-1.23	1.01-1.16	1.04-1.23

*Reference region.

variables in the final model were 13.3%, 55.6%, and 56.7%, respectively. Had we been able to include mammography use and age at menopause in the final model, the results would most likely be similar to those presented above because the effects of these two variables on the MRs were of similar magnitude in opposite directions. After additional adjustment for menopausal estrogen use, the corresponding multivariate MRs were 1.18, 1.06, and 1.09, respectively.

Sensitivity Analyses

Analyses were conducted to determine the extent to which alternative assumptions regarding the magnitude of the RRs for selected factors would alter the main results of this study. RRs that were higher and lower than the estimates used in the main analyses were used in the sensitivity analyses. Age at first live birth was selected for this analysis because adjustment for this variable had a substantial impact on the regional MRs. Years of education was also selected because adjustment for it had a substantial impact on the MR for the West compared with the South, and few data were available in the literature from which to derive an estimate of the mortality risk ratio.

Among women who were younger than age 50 years, using the RRs for age at first live birth of 1.0, 1.0, 1.1, 1.5, 1.6, and 1.5 for the categories specified in Table 3 in the full model in Table 6 yielded MRs of 0.96, 1.05, and 1.03 for the West, Midwest, and Northeast, respectively, compared with the South. Similar analyses using RRs for age at first live birth of 1.0, 1.4, 1.9, 2.8, 3.0, and 2.6 yielded MRs of 0.91, 1.04, and 0.97, respectively. With the use of RRs for education of 1.4, 1.3, 1.2, and 1.0 for the categories specified in Table 3 in the full model, the MRs were 0.91, 1.03, and 0.97, respectively. RRs for education of 3.0, 2.1, 1.6, and 1.0 yielded MRs of 0.97, 1.07, and 1.01, respectively.

Among women who were aged 50 years and older, similar analyses with the use of the same lower estimates for age at first live birth as above yielded MRs of 1.15, 1.11, and 1.18 for the West, Midwest, and Northeast, respectively, compared with the South. Using the higher estimates for age at first live birth, the MRs were 1.12, 1.07, and 1.09, respectively. The percentages of the mortality excess that were explained by the model with the lower estimates for age at first live birth were 0%, 38.9%, and 40% in the West, Midwest, and Northeast, respectively. The corresponding percentages for the model with the higher estimates for age at first live birth were 20%, 61%, and 70%, respectively. Similar analyses with the use of the same lower estimates for education as above yielded MRs of 1.10, 1.08, and 1.12, respectively. With the use of the higher estimates for education, the MRs were 1.17, 1.08, and 1.13, respectively. The percentages of the mortality excess that were explained by the model with the lower estimates for education were 33.3%, 55.6%, and 60.0% in the West, Midwest, and Northeast, respectively. The model with the higher estimates for education explained none of the mortality excess in the West but 55.6% and 56.7% of the mortality excess in the Midwest and Northeast, respectively.

Discussion

During 1950-1954, white women in the Northeast had a 50% higher mortality rate from breast cancer than those in the South (Table 8). The mortality experience of women in the West and Midwest was intermediate between those in the South and Northeast. Between 1950-1954 and 1985-1989, rates among younger women in the South were relatively stable, whereas rates among younger women in the Northeast, West, and Midwest decreased. During the same period, rates among older women in the South increased by 30%, whereas rates among those in the Northeast, West, and Midwest increased by only 10%. Although these patterns have led to increasing geographic homogeneity in breast cancer mortality rates over time, mortality rates among older women in the late 1980s were still highest in the Northeast and lowest in the South. However, among younger women, regional differences in breast cancer mortality rates were less pronounced by the late 1980s.

Table 8. Breast cancer mortality rates* and rate ratios for white women by region, age, and year†

	Age, 20-49 y				Age, 50-79 y				Age, 20-79 y			
Years	S	W	MW	NE	S	W	MW	NE	S	W	MW	NE
1950-1954												
Rate	11.8	13.5	14.1	16.4	59.7	77.8	81.8	90.7	29.8	37.6	39.5	44.3
Rate ratios	1.0‡	1.1	1.2	1.4	1.0‡	1.3	1.4	1.5	1.0‡	1.3	1.3	1.5
1965-1969												
Rate	12.6	13.4	14.3	16.7	67.6	80.0	85.1	94.7	33.2	38.4	40.9	46.0
Rate ratios	1.0‡	1.1	1.1	1.3	1.0‡	1.2	1.3	1.4	1.0‡	1.2	1.2	1.4
1980-1984												
Rate	11.3	11.7	12.4	13.2	74.8	86.3	87.9	97.9	35.2	39.7	40.7	45.0
Rate ratios	1.0‡	1.0	1.1	1.2	1.0‡	1.2	1.2	1.3	1.0‡	1.1	1.2	1.3
1985-1989												
Rate	11.5	11.6	12.3	12.8	78.3	86.6	89.1	99.1	36.6	39.7	41.1	45.2
Rate ratios	1.0‡	1.0	1.1	1.1	1.0‡	1.1	1.1	1.3	1.0‡	1.1	1.1	1.2

*Rate per 100 000.

†Rates are age standardized to the U.S. population by 5-y age groups. Data obtained from the National Center for Health Statistics. S = South; W = West; MW = Midwest; and NE = Northeast.

‡Reference region.

In the present analysis, we examined geographic variation in breast cancer mortality for the year 1987. Before adjustment for regional differences in recognized risk factors and prognostic factors, mortality excesses among younger women in the Northeast, Midwest, and West were less than 10% compared with those in the South. After adjustment, MRs were near unity for all regions. Among older women, the excess mortality was more substantial before adjustment for relevant factors, ranging from 15% in the West to 30% in the Northeast. Approximately 50% of the excesses in the Northeast and Midwest and 10% of the excess in the West could be explained on the basis of regional differences in the prevalence of recognized breast cancer risk factors and prognostic factors. After adjustment for these factors, the magnitude of excess in breast cancer mortality in the Northeast (i.e., 13%) was comparable to that in the West (13%) but still slightly higher than that in the Midwest (8%).

There are a number of potential limitations to the current analysis. Foremost, it is an ecologic analysis involving multiple data sources in which the exposure and outcome information was available for the geographic regions but not for specific individuals. One particular concern is that the menopause variable used in this study was based on regional practices of ovarian removal in 1980. Such practices may not apply to women who experienced their menopause at comparable ages but in earlier years. Another issue is that misspecification of the magnitude of RRs for risk factors whose prevalence varied over the regions could have resulted in either the overestimation or underestimation of our adjusted MRs. Such misspecification could be a consequence of the reliance on incidence RRs for some variables or residual confounding in some RRs. To address this issue, we conducted sensitivity analyses using different RRs for those variables whose prevalence varied most across regions. Results among younger women were unaffected when we used higher and lower RRs for age at first live birth and education. Among older women, we could explain between 40% and 70% of the difference in mortality between the Northeast and South, depending on whether RRs of lower and higher magnitudes for age at first live birth were used in our final model. Inasmuch as the RRs for this variable used in our main analyses were chosen because they were the most representative of the available literature, however, it seems reasonable to assume that the results from our final model are more realistic than those from the various models used to test sensitivity. Changes in the RRs for education had little impact on the MRs, with the exception that higher RRs slightly increased the excess mortality in the West compared with the South. Misspecification of the RRs for other variables that did not vary as much by region would be less likely to have a major impact on our findings.

Because data on interactions among recognized breast cancer risk factors and prognostic factors are scant, we calculated the RRs for a combination of risk factors as the product of RRs for the individual factors. If, however, the combined risk from several factors whose prevalences varied over the regions is not multiplicative or there are population differences in the importance of risk factors, the adjusted MRs could also be too large or too small. Another weakness of this study is that we were unable to consider important variables that could affect breast cancer survival, such as extent of disease at diagnosis and breast cancer treatment. However, we were able to account for two presumed surrogates for these factors, years of education and mammography use.

Despite its limitations, this study represents the most detailed analysis of the difference in breast cancer mortality rates between geographic regions to date. Our results suggest that a considerable proportion of the excess mortality in the Northeast and Midwest could be explained by differences in the prevalence of recognized risk factors and prognostic factors. Regional differences in one or more factors not considered in this study could be responsible for the small excesses that remained among older women in the Midwest, West, and Northeast compared with the South, including exposures to hypothesized environmental factors (e.g., vitamin D, sunlight, organochlorines, and electromagnetic fields), dietary factors, quality of death certificate information, or factors that influence survival from breast cancer (e.g., extent of disease at diagnosis or treatment).

Further studies are needed to address whether differences in the prevalence of recognized risk and prognostic factors contribute to particularly high and low breast cancer mortality rates within the Northeast and other regions of the country.

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Notes

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Induction of T-Cell Immunity Against Ras Oncoproteins by Soluble Protein or Ras-Expressing *Escherichia coli*

*Robert G. Fenton, Christopher J. Keller, Nabil Hanna, Dennis D. Taub**

Background: **Point mutations in the ras proto-oncogene that activate its oncogenic potential occur in approximately 30% of human cancers. Previous studies have demonstrated that T-cell immunity against some forms of mutant Ras proteins could be elicited, and some effectiveness against tumors expressing activated Ras has been reported.** ***Purpose:*** **The goal of this study was to determine if immunization of mice with two forms of mutant Ras protein can induce high levels of Ras mutation-specific T-cell immunity in vitro and tumor regression in vivo.** ***Methods:*** **Mice (BALB/c or C3H/HeJ) were immunized subcutaneously at 2-week intervals with purified Ras oncoproteins mixed with the immunologic adjuvants Antigen Formulation or QS-21, both of which have been shown to enhance the induction of T-cell-mediated immunity when included as components of soluble protein vaccines. In some experiments, mice were immunized directly with heat-killed *Escherichia coli* that had been induced to express one of the mutant Ras proteins. Spleen cells plus lymph node cells from Ras-immunized mice were tested in vitro for lysis of syngeneic Ras-expressing tumor cells and proliferation in response to mutant Ras peptides. For some of the cytolytic activity experiments, the spleen cells were grown under T_H1 conditions (growth in presence of interleukin 2, interferon gamma, and an antibody directed against interleukin 4 to stimulate a cell-mediated immune response) or T_H2 conditions (growth in presence of interleukins 2 and 4 to stimulate a humoral immune response). The specificity of immunity was examined in vivo by challenge of Ras-immunized mice with syngeneic tumor cells expressing mutant Ras oncoproteins (HaBalb, i.e., BALB/c mouse cells expressing Ras with arginine substituted at amino acid position 12 [Arg 12 Ras]; C3HL61, i.e., C3H/HeJ mouse cells expressing Ras with leucine substituted at position 61 [Leu 61 Ras]). Ten mice per group were used in each experiment.** ***Results:*** **Proliferative and cytolytic T-cell responses directed against the Arg 12 Ras protein were generated in BALB/c mice, resulting in protection against challenge with cells expressing Arg 12 Ras and therapeutic benefit in mice bearing established tumors expressing this protein. In C3H/HeJ mice, high levels of cytolytic and proliferative responses were induced against Leu 61 Ras. Immunization with heat-killed *E. coli* genetically engineered to express Leu 61 Ras also led to the induction of anti-Ras T-cell immunity. T cells grown under T_H1 conditions were cytolytic against Ras-transformed tumor cells, whereas those grown under T_H2 conditions were not.** ***Conclusions:*** **Immunization as described here leads to Ras mutation-specific antitumor immunity in vitro and in vivo, with therapeutic efficacy in an established tumor model. [J Natl Cancer Inst 1995;87:1853-61]**

Cancer immunotherapy as a viable form of treatment rests on the suppositions that tumor-specific antigens are expressed by human malignancies and that immune effector mechanisms can be induced to selectively target and destroy tumor cells. The

**Affiliations of authors:* R. G. Fenton, Clinical Research Branch, Division of Clinical Sciences, National Cancer Institute, National Cancer Institute-Frederick Cancer Research and Development Center (NCI-FCRDC), Frederick, MD; C. J. Keller (Biological Carcinogenesis and Development Program), D. D. Taub (Clinical Services Program), Science Applications International Corp., NCI-FCRDC; N. Hanna, IDEC Pharmaceuticals Corp., San Diego, CA.

Correspondence to: Robert G. Fenton, M.D., Ph.D., National Cancer Institute-Frederick Cancer Research and Development Center, P.O. Box B, Bldg. 567, Rm. 207, Frederick, MD 21702.

See "Notes" section following "References."